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(71) Applicant *(for all designated States except US):* AKTIEBOLAGET LEO [SE/SE]; Box 941, S-251 09 Helsingborg (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only) :* FEX, Tomas [SE/SE]; Spårsnögatan 26, S-222 52 Lund (SE). OLSSON, Knut, Gunnar [SE/SE]; Rörsjögatan 10, S-211 37 Malmö (SE). ABRAMO, Aina, Lisbeth [SE/SE]; Järavallsvägen 30 A, S-237 00 Bjärred (SE). CHRISTENSSON, Erik, Gunnar [SE/SE]; Nils Bjelkegatan 3 A, S-222 20 Lund (SE).

(74) Agent: THYLÉN,, Eva; Aktiebolaget Leo, Box 941, S-251 09 Helsingborg (SE).

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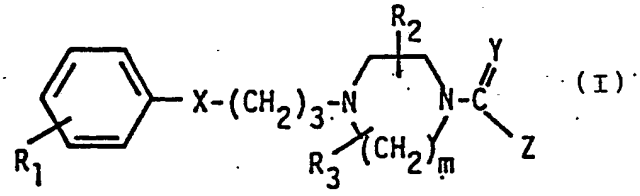
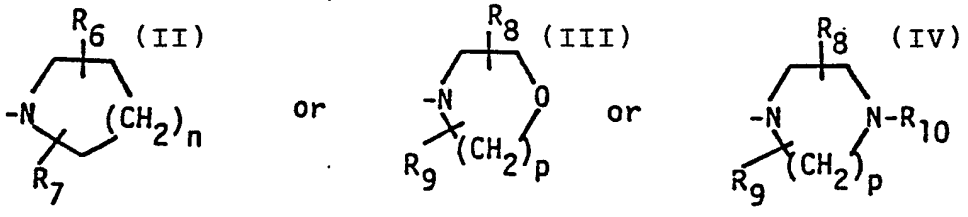
(54) Title: NOVEL PIPERAZINECARBOXAMIDES HAVING A PHENOXYALKYL OR THIOPHENOXYALKYL SIDE CHAIN





(57) Abstract

Novel compounds of formula (I), wherein R_1 is selected from hydrogen, halogen; or trifluoromethyl; X is oxygen or sulfur; R_2 and R_3 are the same or different and selected from hydrogen or lower alkyl; m is 2 or 3; Y is oxygen or sulfur; Z is selected from : $-NR_4R_5$, formulae (II), (III) or (IV), wherein R_4 and R_5 are the same or different and selected from hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy-alkyl, alkoxyalkyl or alkanoyloxyalkyl, phenyl or phenyl-alkyl, wherein the phenyl groups may be unsubstituted or monosubstituted with halogen or CF_3; n is 0, 1, 2 or 3; R_6 and R_7 are the same or different and selected from hydrogen, lower alkyl, hydroxy, lower alkoxy or lower alkanoyloxy; p is 2 or 3; R_8 and R_9 are the same or different and selected from hydrogen or lower alkyl; R_{10} is hydrogen, lower alkyl or lower alkanoyl. The new compounds can be used for treating mental disorders.

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Novel piperazinecarboxamides having a phenoxyalkyl or thiophenoxyalkyl side chain.

Background of the Invention

Drugs in use today for the treatment of mental disorders most often are associated with serious side effects. Antipsychotic drugs commonly cause disturbing extrapyramidal symptoms, and long term treatment may result in tardive dyskinesia. Antidepressants often exhibit cardiotoxicity, and anxiolytic drugs have addicting properties. As a result of these drawbacks efforts are being made to find new pharmacologically active drugs which have fewer side effects.

The present invention relates to novel piperazine- and homopiperazine-carboxamides bearing a phenoxyalkyl or thiophenoxyalkyl side chain, which exhibit valuable pharmacological properties, and which have a low tendency to cause side effects.

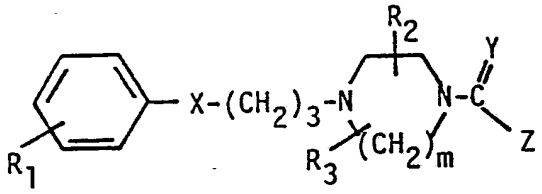
Pharmacologically valuable piperazine-carboxamides are previously known from British patent application No. 2,037,745. However, the compounds according to the British application differ from the compounds according to the present invention in being substituted in the 4-position with a very lipophilic 4,4-diphenylbutyl group. Furthermore, these previous compounds are very active in pharmacological models which may indicate potentation of noradrenaline and serotonine (e.g. inhibition of muricide behaviour), which in turn may cause unwanted side effects, e.g. aneroxigenic. The compounds of the present invention are considerably less active in these pharmacological models indicating that fewer side effects are to be expected when compounds according to the present invention are used.

Piperazinecarboxamides substituted in the 4-position with a butyrophenone side chain are known from Collect.Czech.Chem.Commun 1975, 40(4), 1218-30. The butyrophenone side chain is chemically distinctly different from a phenoxyalkyl or thiophenoxyalkyl group. Besides, the authors state that their compounds display CNS-activity only at high doses.

The French patent application 2367067 and the Swedish patent application 8100852-6 describe piperazine derivatives having a phenoxyalkyl side chain but in neither case are the compounds piperazinecarboxamides. The compounds according to the French patent application are characterized by an analgesic effect that is not accompanied by any secondary effects (cf. the French application page 1, lines 20-24).

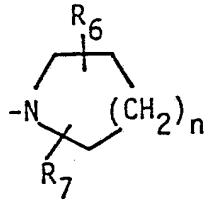
Description of the invention

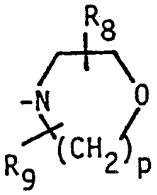
According to the invention there are provided novel compounds having the general formula:

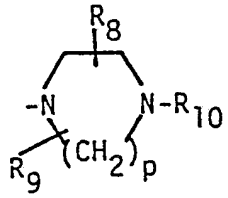


(I)

wherein R_1 is selected from hydrogen, halogen or trifluoromethyl;
X is oxygen or sulfur;
R_2 and R_3 are the same or different and selected from hydrogen or lower alkyl;
m is 2 or 3;
Y is oxygen or sulfur;
Z is selected from: $-NR_4R_5$ or







wherein R_4 and R_5 are the same or different and selected from hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy-alkyl, alkoxyalkyl, alkanoyloxyalkyl: phenyl or phenyl-alkyl, wherein the phenyl groups may

be unsubstituted or monosubstituted with halogen or CF_3;
n is 0, 1, 2 or 3;
R_6 and R_7 are the same or different and selected from hydrogen, lower alkyl, hydroxy, lower alkoxy or lower alkanoyloxy;
p is 2 or 3;
R_8 and R_9 are the same or different and selected from hydrogen or lower alkyl;
R_{10} is hydrogen, lower alkyl or lower alkanoyl, and the pharmaceutically active salts thereof,
and when used in the foregoing definitions the term alkyl is meant to include straight and branched, saturated and unsaturated hydrocarbon groups having from 1 to 10 carbon atoms;
the term cycloalkyl is meant to include cyclic, saturated and unsaturated hydrocarbon groups having from 3 to 8 carbon atoms; the term alkoxy is meant to include straight and branched, saturated or unsaturated alkoxy groups having from 1 to 10 carbon atoms;
the term alkanoyloxy is meant to include straight and branched, saturated and unsaturated alkanoyloxy groups having from 1 to 10 carbon atoms;
the term lower is used when the groups mentioned above contain from 1 to 4 carbon atoms and
the term halogen is meant to include fluoro, chloro and bromo.

The compounds of formula (I) have basic properties and consequently they may be converted to their therapeutically active acid addition salts by treatment with appropriate acids; e.g. inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric and phosphoric acid, or organic acids such as acetic, propanoic, glycolic, lactic, malonic, oxalic, succinic, fumaric, tartaric, citric and pamoic acid.

Conversely, the salt form can be converted into the free base form by treatment with alkali.

In the compounds of the general formula (I) it is preferred that R_1 is halogen or CF_3 and that R_1 is situated in the m- or p-position.

If selected from halogen it is preferred that R_1 is F or Cl, especially F.

When R_1 is CF_3 it is preferably situated in the m-position.

It is preferred that X is oxygen, and that R_2 and R_3 are hydrogen.

When R_2 and R_3 are lower alkyl, methyl and ethyl are preferred, especially methyl.

It is preferred that m=2.

It is preferred that Y is oxygen.

When Z is NR_4R_5 those compounds are preferred wherein R_4 and R_5 together contain less than ten carbon atoms.

Also, as regards the substituents R_4 and R_5 those compounds are preferred wherein R_4 and R_5 are selected from hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl and hydroxyalkyl, especially alkyl and cycloalkyl.

As regards the substituents R_6 and R_7 it is preferred that one of them is hydrogen and the other hydrogen or lower alkyl.

As regards the substituents R_8 and R_9 those compounds are preferred wherein both of them are hydrogen.

When Z is a heterocyclic ring containing two heteroatoms, it is preferred that one of the heteroatoms is oxygen.

Also as regards Z it is preferred that Z does not contain any asymmetric carbon atoms.

The following compounds are preferred:

4-/3-(p-fluorophenoxy)propyl/-N-methyl-1-piperazinecarboxamide
4-/3-(p-fluorophenoxy)propyl/-N-ethyl-1-piperazinecarboxamide
4-/3-(p-fluorophenoxy)propyl/-N-cyclopropyl-1-piperazinecarboxamide
4-/3-(m-trifluoromethyl-phenoxy)propyl/-N-ethyl-1-piperazinecarboxamide
4-/3-(p-fluorophenoxy)propyl/-N-methyl-1-piperazinethiocarboxamide
4-/3-(p-fluorothiophenoxy)propyl/-N-methyl-1-piperazinecarboxamide
4-/3-(p-fluorothiophenoxy)propyl/-N-ethyl-1-piperazinecarboxamide
4-/3-(p-fluorothiophenoxy)propyl/-N-cyclopropyl-1-piperazinecarboxamide
4-/3-(p-fluorothiophenoxy)propyl/-N-methyl-1-piperazinethiocarboxamide
4-/3-(p-fluorophenoxy)propyl/-N,N-dimethyl-piperazinecarboxamide
1-morpholinocarbonyl-4-/3-(p-fluorophenoxy)propyl/-piperazine

Compounds wherein one or both of R_2 and R_3 are alkyl are racemic mixtures, and these may consequently be resolved into enantiomers.

The compounds of formula (I) and their pharmaceutically acceptable salts have valuable pharmacological properties making them useful for treatment of mental disorders such as psychoses, depression and anxiety. For example they may be useful for the prophylaxis and/or treatment of schizophrenia, mania or senile, involutional or organic psychoses as well as depressive psychoses, depression and anxiety.

Psychosomatic disorders caused by anxiety and stress should be alleviated by compounds of formula (I).

The new compounds may also be used in the prophylaxis and treatment of aggressive behaviour, which may be associated with mentally retarded and/or behaviourally disturbed patients and other form of aggression of either known or unknown etiology.

The new compounds may be useful in the treatment of aggressive behaviour in animals, especially in pigs, and also in promoting the development of a natural hierarchy in groups of animals without bursts of aggression and in calming of anxious and stressed animals.

The compounds of formula (I) have a clear limbic profile of action and are thus not likely to cause extrapyramidal side effects. This is evidenced by their ability to inhibit amphetamine induced locomotion in mice, whereas they do not block amphetamine induced stereotypies. Their ability to inhibit isolation induced aggression in male mice is also the result of activity in limbic brain areas. Extrapyramidale side effects are highly undesirable and are commonly seen with antipsychotics in clinical use today.

Effective quantities of any of the foregoing pharmacologically active compounds of formula (I) may be administered to a human being or an animal for therapeutic purposes according to usual routes of administration and in usual forms, such as orally in solutions, emulsions, suspensions, pills tablets and capsules, in pharmaceutically acceptable carriers and parenterally in the form of sterile solutions. For the parenteral administration of the active substance the carrier of excipient may be a sterile, parenterally acceptable liquid, e.g. water, or a parenterally acceptable oil, e.g. arachidic oil.

The compounds of formula (I) may if desired be administered in various slow release formulations.

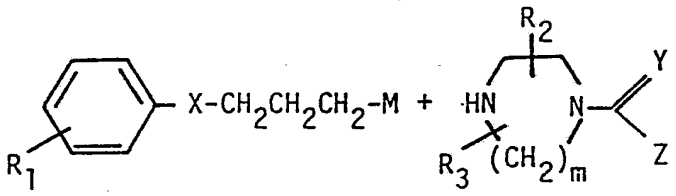
Although very small quantities of the active materials of the present invention are effective when minor therapy is involved or in the cases of administration to subjects having a relatively low body weight, unit dosages are usually from 2 milligrams upwards, preferably 25, 50 or 100 milligrams or even higher depending on the condition to be treated and the age and weight of the patients as well as the response to the medication.

The unit dose may be from 0.1 to 200 milligrams, preferably from 10 to 50 milligrams. Daily dosages should preferably range from 10 milligrams to 400 milligrams. The exact individual dosages as well as daily dosages will, of course, be determined according to standard medical principles under the direction of a physician or veterinarian.

Methods of preparation

The compounds having the general formula (I) may be prepared by conventional methods.

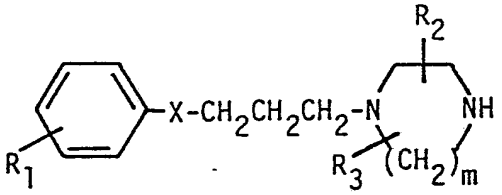
Method 1



II III

A compound of formula II, wherein R_1 and X are as defined above, and wherein M is a suitable leaving group such as halogen and alkyl- or arylsulfonate is reacted with a compound of formula (III) wherein R_2, R_3, Y, Z and m are as defined previously. The reactions may be carried out using standard N-alkylating procedures.

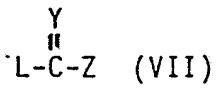
Method 2



IV

R_4-NCO (V)

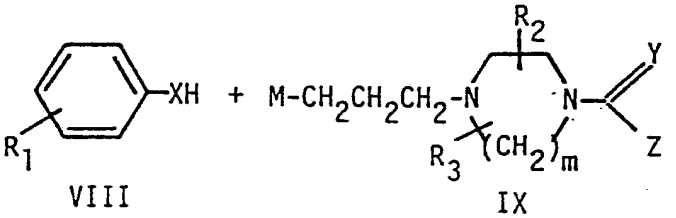
R_4-NCS (VI)



(VII)

A compound of formula (IV), wherein R_1, X, R_2, R_3 and m are as defined above, is reacted with an isocyanate of formula (V) or an isothiocyanate of formula (VI) or a carbamoyl derivative of formula (VII), wherein R_4, Y and Z are as previously defined, and wherein L is a suitable leaving group such as halogen, phenoxy and substituted phenoxy (e.g. p-nitrophenoxy). The reactions may be carried out using standard procedures. The addition of an appropriate base may in some instances facilitate the reaction, and may if acid is formed during the reaction serve to neutralize this.

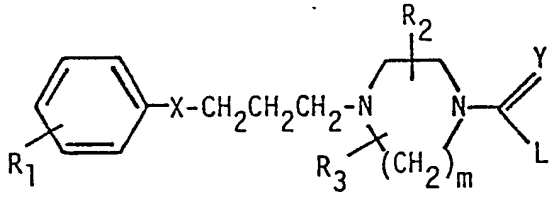
Method 3



VIII IX

A compound of formula (VIII) wherein R_1 and X are as previously defined is reacted with a compound of formula (IX) wherein M, R_2, R_3, m, Y and Z are as defined previously. The reaction is carried out using standard phenolate or thiophenolate alkylating conditions.

Method 4

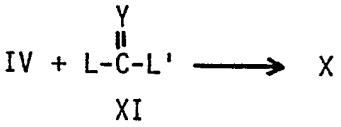


X

A compound of formula (X) wherein R_1, X, R_2, R_3, m, Y and L are as defined above is reacted with a compound of formula Z-H wherein Z is as previously defined. The reaction is carried out using standard procedures. When L is a poor leaving group and/or when Z-H is a poor nucleophile it may be advantageous to use a large excess of Z-H and/or to heat the reaction mixture for a longer period of time.

The intermediate X may be prepared by standard procedures according to:

Method 5

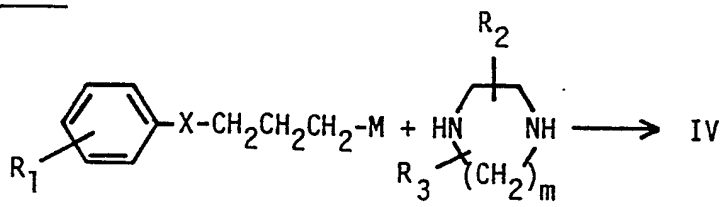


XI

A compound of formula IV is reacted with a compound of formula XI wherein L and Y are as previously defined, and L' is a suitable leaving group such as halogen, phenoxy and substituted phenoxy (e.g. p-nitrophenoxy). Most commonly at least one of L and L' is halogen. The reaction is preferably performed in an inert solvent, and an appropriate base may be added to take care of the acid formed during the reaction.

The intermediate IV may be prepared by conventional methods according to:

Method 6



II

A compound of formula II is reacted with an excess of amine, wherein R_2 and R_3 are as defined above, using standard N-alkylating conditions.

Examples

The following examples are intended to illustrate but not to limit the scope of the invention, although the compounds named are of particular interest for our intended purposes. These compounds have been designated by a number code, a:b, where "a" means the number of the example wherein the preparation of the compound in question is described, and "b" refers to the order of the compounds prepared according to that example. Thus, compound 1:2 means the second compound prepared according to Example 1.

The structures of the compounds are confirmed by NMR, mass spectra and elementary analysis. When melting points are given, these are uncorrected.

Example 1

3.6 g (0.015 mole) of 1-/3-(p-fluorophenoxy)propyl/-piperazine was dissolved in 20 ml of toluen and cooled in an ice bath. 0.9 g (0.015 mole) of methylisocyanate dissolved in 35 ml of toluene was added dropwise during 15 minutes. The reaction mixture was allowed to reach room temperature and the solvent was subsequently removed by evaporation. The residue was recrystallized from toluene/ligroin to yield 4.2 g of 4-/3-(p-fluorophenoxy)propyl/-N-methyl-1 piperazinecarboxamide (1:1), M.p. 122-23°C.

The corresponding hydrochloride (1:2) was prepared by dissolving 4.0 g of the base in ether/abs.ethanol and adding and excess of HCl in ethanol. The hydrochloride which precipitated was recrystallized from abs.ethanol. Yield 3.6 g, m.p. 222-24°C.

Using essentially the same procedure the following compounds are prepared (isolated as the free bases or as the corresponding salts) from the corresponding starting materials.

1:3 4-/3-(p-fluorophenoxy)propyl/-N-ethyl-1-piperazinecarboxamide hydrochloride, m.p. 211-12°C

1:4 4-/3-(p-fluorophenoxy)propyl/-N-cyclopropyl-1-piperazinecarboxamide hydrochloride, m.p. 217-18°C

1:5 4-/3-(p-fluorophenoxy)propyl/-N-(1-methylethyl)-1-piperazinecarboxamide

1:6 4-/3-(p-fluorophenoxy)propyl/-N-hexyl-1-piperazinecarboxamide

1:7 4-/3-(p-fluorophenoxy)propyl/-N-cyclohexyl-1-piperazinecarboxamide

1:8 4-/3-(p-fluorophenoxy)propyl/-N-(2-propenyl)-1-piperazinecarbox-

amide

1:9 4-/3-(p-chlorophenoxy)propyl/-N-ethyl-1-piperazinecarboxamide

1:10 4-/3-(m-trifluoromethyl-phenoxy)propyl/-N-ethyl-1-piperazine-carboxamide hydrochloride, m.p. 196-98°C

1:11 4-(3-phenoxypropyl)-N-ethyl-1-piperazinecarboxamide

1:12 4-/3-(p-fluorophenoxy)propyl/-N-methyl-1-piperazinethiocarbox-amide hydrochloride, m.p. 182-83°C

1:13 4-/3-(p-fluorothiophenoxy)propyl/-N-ethyl-1-piperazinecarbox-amide hydrochloride, m.p. 195-7°C

1:14 4-/3-(p-fluorothiophenoxy)propyl/-N-cyclopropyl-1-piperazine-carboxamide

1:15 4-/3-(p-fluorothiophenoxy)propyl/-N-methyl-1-piperazinethio-carboxamide

1:16 4-/3-(p-fluorophenoxy)propyl/-2,5-trans-dimethyl-N-ethyl-1-piperazinecarboxamide

1:17 4-/3-(p-fluorophenoxy)propyl/-2,5-trans-dimethyl-N-cyclo-propyl-1-piperazinecarboxamide

1:18 4-(3-phenoxypropyl)-2,5-trans-dimethyl-N-(1-methylethyl)-1-piperazinecarboxamide hydrochloride, m.p. 185-6°C

1:19 4-/3-(p-fluorophenoxy)propyl/-N-ethyl-1-(1,4-diazacycloheptane-carboxamide)

1:20 4-/3-(p-fluorophenoxy)propyl/-N-cyclohexyl-1-(1,4-diazacyclo-heptanecarboxamide) hydrochloride, m.p. 221-4°C (dec.)

1:21 4-/3-(p-fluorothiophenoxy)propyl/-N-ethyl-1-(1,4-diazacyclo-heptanecarboxamide)

1:22 4-/3-(p-fluorophenoxy)propyl/-N-phenyl-1-piperazinecarboxamide, hydrochloride, m.p. 202-3°C

1:23 4-/3-(p-fluorophenoxy)propyl/-N-p-chlorophenyl-1-piperazine-carboxamide

1:24 4-/3-(p-fluorophenoxy)propyl/-N-phenylmethyl-1-piperazinecarbox-amide

Example 2

7.0 g (0.03 mol) of 1-/3-(p-fluorophenoxy)propyl/-piperazine was dissolved in 45 ml of conc. acetic acid. 3.2 g (0.04 mol) KOCN was dissolved in 20 ml of H_2O and added to the reaction mixture which subsequently was stirred (for) 20 h. at RT. After cooling to 0°C the reaction mixture was made basic by addition of 5N NaOH. The product separated slowly by crystallization and was filtered off. It was dissolved in CH_2Cl_2 and the solution was washed with H_2O, dried with Na_2SO_4,

and the solvents evaporated. The residual oil crystallized and was recrystallized from toluene/ligroin to yield 5.9 g of 4-/3-(p-fluorophenoxy)propyl/-1-piperazine carboxamide (2:1), m.p. 98-100°C.

The corresponding hydrochloride was prepared by dissolving 5.5 g of the base in 50 ml of a mixture of abs. ethanol/ether. Addition of an excess of HCl in ethanol and additional ether precipitated the hydrochloride. After recrystallization from isopropanol 4.7 g of the hydrochloride (2:2) was obtained, m.p. 209-10°C.

Using essentially the same procedure (heating of the reaction mixture is required) the following compound is prepared from the corresponding starting materials:

2:3 4-/3-(p-fluorophenoxy)propyl/-1-piperazinethiocarboxamide

Example 3

12.5 g (0.031 mol) of p-nitrophenyl-4-/3-(p-fluorophenoxy)propyl/-1-piperazine carboxylate was stirred in a mixture of 20 ml of dimethylamine and 20 ml of THF at 0°C for 3 days. The reaction mixture was partitioned between ether and H_2O. The ether phase was washed twice with a Na_2CO_3 solution and twice with a NaCl-solution. The mixture was dried with Na_2SO_4. After filtration excess of HCl in ethanol was added to precipitate the hydrochloride. After filtration and recrystallization from ethyl acetate/ ethanol was obtained 5.5 g of 4-/3-(p-fluorophenoxy)propyl/-N,N-dimethyl-1-piperazinecarboxamide, hydrochloride (3:1), m.p. 185-7°C.

Using essentially the same procedure (sometimes omitting the co-solvent THF and heating in the case of more unreactive amines) the following compounds were prepared (isolated as the free bases or as the corresponding salts) from the corresponding starting materials.

3:2 1-morpholinocarbonyl-4-/3-(p-fluorophenoxy)propyl/-piperazine, hydrochloride, m.p. 192-3°C

3:3 1-pyrrolidinocarbonyl-4-/3-(p-fluorophenoxy)propyl/-piperazine

3:4 1-piperidinocarbonyl-4-/3-(p-fluorophenoxy)propyl/-piperazine

3:5 1-(4-methylpiperidinocarbonyl)-4-/3-(p-fluorophenoxy)propyl/-piperazine, hydrochloride, m.p. 216-17°C

3:6 1-(4-hydroxy-piperidinocarbonyl)-4-/3(p-fluorophenoxy)propyl/-piperazine

3:7 1-(4-methyl-piperazinocarbonyl)-4-/3-(p-fluorophenoxy)propyl/-piperazine

3:8 1-(4-acetyl-piperazinocarbonyl)-4-/3-(p-fluorophenoxy)propyl/-piperazine

3:9 4-/3-(p-fluorophenoxy)propyl/-N-(2-hydroxyethyl)-1-piperazine-carboxamide, hydrochloride, m.p. 186-7°C

Example 4

25 g (0.105 mol) of 1-/3-(p-fluorophenoxy)propyl/-piperazine was dissolved in 300 ml of toluene, 20 ml of triethylamine was added and the mixture was cooled to 0°C. 21.2 g (0.105 mol) of p-nitrophenyl-chloroformate in 300 ml of toluene was added dropwise. The reaction mixture was stirred at RT for 3 h. The triethylamine hydrochloride was filtered off and the solvents were evaporated. The residue was dissolved in methanol and the product was allowed to crystallize overnight. The product was filtered off to yield 25 g of p-nitrophenyl-4-/3-(p-fluorophenoxy)propyl/-1-piperazine-carboxylate (4:1), m.p. 101-02°C.

Example 5

82 g (0.43 mol) of 1-chloro-3-(p-fluorophenoxy)-propane and 262 g of piperazine were dissolved in 700 ml of isopropanol and refluxed for 16 h. The reaction mixture was allowed to reach RT and piperazine which had precipitated was filtered off. The solvents were evaporated and the residue was dissolved in CH_2Cl_2. After washing with sat. NaCl-solution and drying with Na_2SO_4 the CH_2Cl_2 was evaporated and the residue destilled to yield 75 g of 1-/3-(p-fluorophenoxy)propyl/-piperazine (5:1), b.p. 104-6°C (0.05 mm Hg).

Example 6

This example illustrates the potency of compounds of formula (I) and their pharmaceutically active acid addition salt for treatment of mental disorders.

Test: Isolation induced aggressive behaviour test

Male mice subjected to prolonged isolation develop aggressive behaviour against each other when paired (Yen, C.Y. et al., Arch.Int.Pharmacodyn. 123, 179, (1959): Valzelli, L., Adv.Pharmacol. 5, 79 (1967). All clinically used neuroleptics and antidepressants studied in this test inhibit this aggressive behaviour although their activity may differ. Also anxiolytic drugs, e.g. diazepam, are active on this kind of aggressive behaviour. The clinical correlation of this test indicates tranquillizing and anxiolytic activities as well as antiagggressive properties as such (Duncan, R.L. et al., J Med.Chem. 13, 1 (1970)).

This type of aggression is interesting because it is known that this kind of emotional behaviour might be located in limbic structures

in the brain (MacLean, P.D., Psychosom.Med. 11, 338 (1949)).

Every week male NMRI mice, weighing 20-22 g, were isolated in Makrolon cages for three weeks with diet and water ad libitum. A piece of cardboard was placed between the cages to prevent visual contact.

To test aggressiveness the mice were paired in a neutral area, a beaker (14 cm high and diameter 14 cm). A pair is considered aggressive if both the animals show clear signs of fighting within 5 minutes. This fighting is characterized by biting and vocalization. As soon as fighting is seen, the mice are separated and brought to their home cage (every second mouse is marked). If only one of two mice exhibit aggressive behaviour the aggressive one is paired with another to make a well matched, aggressive pair. Animals showing no aggression are discarded.

The frequency of paired mice exhibiting fighting varies from 50-100 per cent depending on the time of the year. The test substance is administered s.c. (0.2-0.4 ml/20 g). The mice are paired 0.5 hour after the injection for trials of 5 minutes' duration.

The ED_{50}-value (mg/kg) reported is the dose inhibiting aggressive behaviour among 50 per cent of the pairs 0.5 hour after drug administration.

Table

Isolation induced aggressive behaviour test

Compound	ED_{50} mg/kg s.c.
1:3	5
Thioridazine[a)]	5
Diazepam[b)]	6.7

a) Merck Index, 10th Ed., 9202
b) " " " " 2967

Example 7

The following formulations are representative for all of the pharmacologically active compounds of this invention. Example of a suitable capsule formulation:

	Per capsule, mg
Active ingredient, as salt	10
Lactose	250
Starch	120
Magnesium stearate	5
Total	385

In case of higher amounts of active ingredient, the amount of lactose used may be reduced.

Example of a suitable tablet formulation:

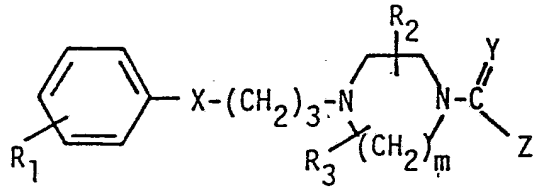
	Per tablet, mg
Active ingredient, as salt	10
Potato starch	90
Colloidal silica	10
Talc	20
Magnesium stearate	2
5% aqueous solution of gelatin	25
Total	157

Solutions for parenteral applications by injection can be prepared in an aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substance preferably in a concentration of from about 0.5% to about 5% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules.

The pharmaceutical preparations may also contain therapeutically useful substances other than the pharmacologically active compounds of formula (I).

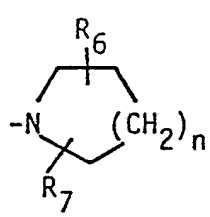
CLAIMS

1. Novel compounds having the general formula:

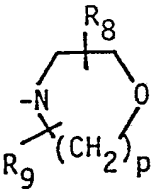


(I)

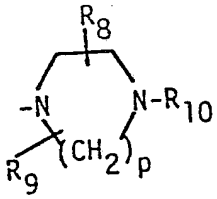
wherein R_1 is selected from hydrogen, halogen or trifluoromethyl;
X is oxygen or sulfur;
R_2 and R_3 are the same or different and selected from hydrogen or lower alkyl;
m is 2 or 3;
Y is oxygen or sulfur;
Z is selected from:
$-NR_4R_5$ or



or



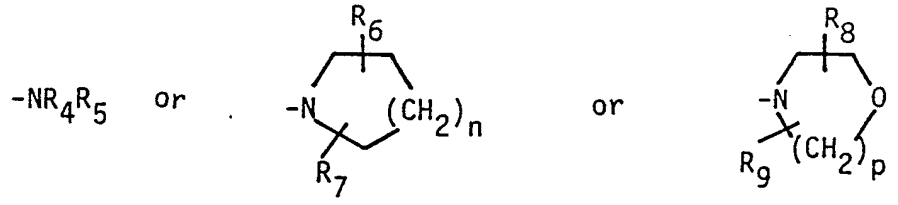
or



wherein R_4 and R_5 are the same or different and selected from hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy-alkyl, alkoxyalkyl or alkanoyloxyalkyl, phenyl or phenyl-alkyl, wherein the phenyl groups may be unsubstituted or monosubstituted with halogen or CF_3;
n is 0, 1, 2 or 3;
R_6 and R_7 are the same or different and selected from hydrogen, lower alkyl, hydroxy, lower alkoxy or lower alkanoyloxy;
p is 2 or 3;
R_8 and R_9 are the same or different and selected from hydrogen or lower alkyl;
R_{10} is hydrogen, lower alkyl or lower alkanoyl,
wherein the term alkyl is meant to include straight and branched, saturated and unsaturated hydrocarbon groups;
the term cycloalkyl is meant to include cyclic, saturated and un-

saturated hydrocarbon groups;
the term alkoxy is meant to include straight and branched, saturated or unsaturated alkoxy groups and
the term alkanoyloxy is meant to include straight and branched, saturated and unsaturated alkanoyloxy groups
and the pharmaceutically active salts thereof.

2. A compound according to claim 1 characterized in that Z is selected from the group consisting of

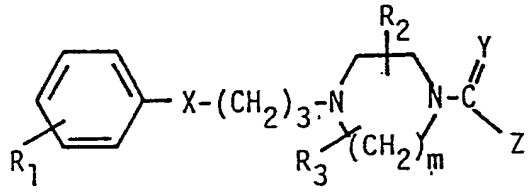


R_4 and R_5 are selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl and hydroxy-alkyl;
one of R_6 and R_7 is hydrogen and the other is hydrogen or lower alkyl;
and that R_8 and R_9 are hydrogen.

3. A compound according to claim 1 or 2 characterized in that R_2 and R_3 are hydrogen.
4. A compound according to any of the claims 1-3 characterized in that m=2.
5. A compound according to any of the claims 1-4 characterized in that X and Y are oxygen.
6. A compound according to claim 1-5 characterized in that R_1 is F.
7. A compound according to claim 1 selected from the following group:
4-/3-(p-fluorophenoxy)propyl/-N-methyl-1-piperazinecarboxamide
4-/3-(p-fluorophenoxy)propyl/-N-ethyl-1-piperazinecarboxamide
4-/3-(p-fluorophenoxy)propyl/-N-cyclopropyl-1-piperazinecarboxamide
4-/3-(m-trifluoromethyl-phenoxy)propyl/-N-ethyl-1-piperazinecarboxamide
4-/3-(p-fluorophenoxy)propyl/-N-methyl-1-piperazinethiocarboxamide
4-/3-(p-fluorothiophenoxy)propyl/-N-methyl-1-piperazinecarboxamide
4-/3-(p-fluorothiophenoxy)propyl/-N-ethyl-1-piperazinecarboxamide
4-/3-(p-fluorothiophenoxy)propyl/-N-cyclopropyl-1-piperazinecarboxamide
4-/3-(p-fluorothiophenoxy)propyl/-N-methyl-1-piperazinethiocarboxamide

4-/3-(p-fluorophenoxy)propyl/-N,N-dimethyl-1-piperazinecarboxamide
1-morpholinocarbonyl-4-/3-(p-fluorophenoxy)propyl/-piperazine

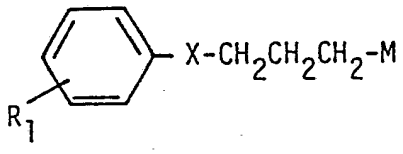
8. A method for the preparation of a compound having the general formula I



(I)

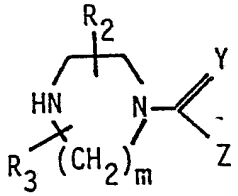
wherein R_1, R_2, R_3, X, Y, Z and m are as defined in claim 1, characterized by

a) reacting a compound



II

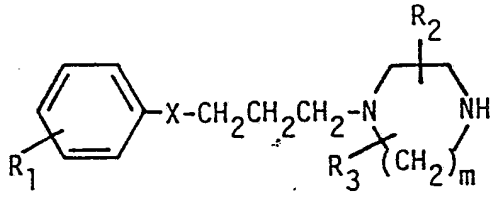
wherein X and R_1 are as defined above and M is a leaving group, with a compound



III

wherein R_2, R_3, Y, Z and m are as previously defined,

b) reacting a compound

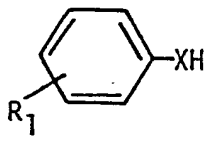


IV

wherein R_1, R_2, R_3, X and m are as previously defined, with an isocyanate, R_4-NCO (V), wherein R_4 is as previously defined, or

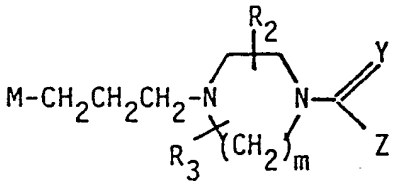
an isothiocyanate, R_4-NCS, (VI), wherein R_4 is as previously defined, or a carbamoyl derivative, L-CY-Z (VII) wherein Y and Z are as previously defined and L is a leaving group,

c) reacting a compound



VIII

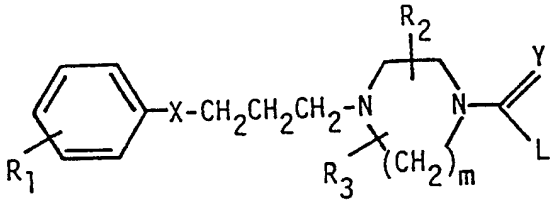
wherein R_1 and X are as previously defined, with a compound



IX

wherein M, R_2, R_3, m, Y and Z are as previously defined, or

d) reacting a compound



X

wherein R_1, R_2, R_3, m, X, Y and L are as previously defined with a compound Z-H, wherein Z is as previously defined.

9. Pharmaceutical compositions containing as an active ingredient one or more of the compounds having the general formula (I), preferably together with a pharmaceutically acceptable carrier and, if desired, other pharmacologically active agents.

10. A method of treating a living animal body suffering from a mental disorder which comprises the step of administering to said living animal body a compound having the general formula (I).

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE86/00038

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC 4

C 07 D 295/14, 241/04, 243/08, 401/06, 413/06, A 61 K 31/495

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC 4	C 07 D 241/04, 243/06-/08, 295/14, /16, /18, 401/06, 403/04, 413/06; A 61 K 31/495
IPC 2	A 61 k 27/00, C 07 d 31/70 .../...

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

SE, NO, DK, FI classes as abvove

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	Chemical Abstracts, vol 83, (1975) Abs No 131539U, Collect Czech Chem Commun, 40 (4), 1218-30 (Eng)	1-10
X	Chemical Abstracts, vol 85 (1976) Abs No 33 082 m, Kyorin Pharmaceutical Co Ltd Japan Kokai 76 08, 283	1-10
X	EP, A3, 0 080 992 (AB FERROSAN) 8 June 1973 & WO, 83/01950 AU, 10152/83	1-10
X	GB, A, 2 037 745 (AB FERROSAN) 16 July 1980 & LU, 81807 BE, 879528 NL, 7907741 FR, 2439187 DE, 2941880 AU, 51984/79 SE, 7908701 US, 4447433	1-10

.../...

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1986-04-24	1986-05-05
International Searching Authority	**Signature of Authorized Officer**
Swedish Patent Office	Niklas Forslund Niklas Forslund

MJ

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

II Fields Searched (cont)

US Cl 260: 208
544: 258, 259, 260, 372, 386, 390, 398, 399, 400, 406

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers....., because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	CH, 643247 AT, 376666	
X	FR, A1, 2 367 067 (KYORIN PHARMACEUTICAL CO LTD) 5 May 1978 & BE, 859439 DE, 2745073 JP, 53046988 SE, 7711246	1-10
A	SE, A, 8100852-6 (TANABE SEIYAKU CO LTD) 18 August 1981	1-10
A	SE, A, 8300987-8 (DELALANDE SA) 27 August 1983	1-10
A	EP, A1, 0 042 366 (AB FERROSAN) 8 June 1983	1-10
A	US, A, 3 962 249 (KYORIN SEIYAKU KABU-SHIKI) 8 June 1976	1-10
A	US, A, 3 000 892 (P A JANSSEN) 19 September 1961	1-10